RIFAMPIN: CLINICAL EXPERIENCE WITH A NEW ANTI-TUBERCULOSIS DRUG

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Rifampin (Figure 1) is a semisynthetic derivative of rifamycin SV, an antibiotic isolated from Streptomyces Mediterranei in the laboratories of Lepetit, Milan, Italy. The drug has a rather broad spectrum of antimicrobial activity *in vitro* (Table 1), being most effective against gram positive cocci, Mycobacterium tuberculosis, and certain gram negative cocci such as Neisseria meningitidis. It is less effective against gram negative bacteria generally, and its activity against mycobacteria other than M. tuberculosis varies from "high" against M. Kansasii and M. phlei, "variable" to "low" against M. intracellulare, to definitely "low" against M. fortuitum and most rapid growers. It is virtually inactive against Nocardia, actinomyces and most pathogenic fungi. *In vitro* activity against certain viruses has been demonstrated. The drug acts through inhibition of DNA dependent RNA polymerase of susceptible bacterial cells. Unlike the parent rifamycins, it is readily absorbed from the gastrointestinal tract after oral administration and readily reaches serum concentrations 10–50 times above the minimal inhibitory concentration *in vitro* for M. tuberculosis (Figure 2). The peak serum concentration is reached within 2–3 hours following oral administration of a single 600 mg. dose to fasting subjects. The presence of food in the stomach tends to lower the serum concentrations and delay the peak. The drug is excreted primarily through the biliary tract and kidneys, and has been detected in most tissues and body fluids in concentrations above the M.I.C. for susceptible organisms.

Encouraged by reports from abroad, principally Italy, Belgium and France, a cooperative pilot study was undertaken in April 1968 in 6 Veterans Administration hospitals. Patients selected were those with advanced tuberculosis which had failed to be controlled with conventional drug regimens available at that time. The majority yielded organisms resistant to 3 or more anti-tuberculosis drugs and were considered difficult therapeutic challenges to any regimen. The single regimen employed was rifampin 600 mg. plus ethambutol 15 mg./kg., both given in a single daily dose before breakfast. Table 2 shows the susceptibility of pretreatment cultures to rifampin for the first 40 patients treated in this study. Seventy-five per cent

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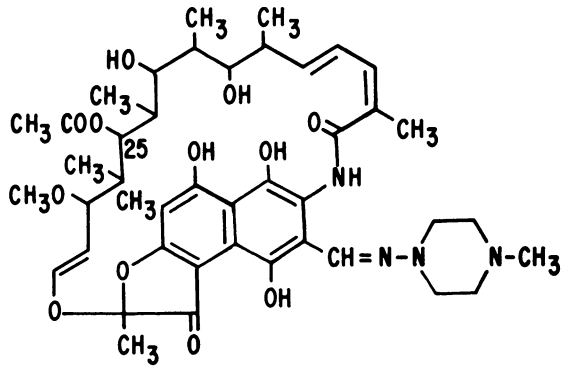

Rifampin

3-(4-Methylpiperazinyl-iminomethyl) rifamycin SV

FIG. 1. Structural Formula of Rifampin.

showed complete inhibition in 0.2 mcg./ml. on 7H10 medium, and all were inhibited by 1.0 mcg./ml. All showed complete inhibition in 5 mcg./ml. of ethambutol. In Figure 3 are seen the serum concentrations of rifampin in our patients 4 hours after the initial 600 mg. dose on day 1. The ordinate shows the serum concentration in mcg./ml. The abscissa shows the 600 mg. dose converted to the dose in mg./kg. of body weight for each patient. The mean serum concentration was approximately 8 mcg./ml., which probably

TABLE 1

Rifampin—In Vitro *Activity*

Organism	Medium	M.I.C. mcg./ml.
Staph. aureus	Penassay Br.	.002–.005
Staph. albus	Penassay Br.	.002
Strep. fecalis	Penassay Br.	.01–.05
Strep. hemolyticus	Brain Ht. Inf.	.02
D. pneumoniae	Brain Ht. Inf.	.01
N. gonorrhea	Trypt. Phos	.02
N. meningitidis	Trypt. Phos.	.1
E. coli	Penassay Br.	1.0–10.0
Pseud. aerugin	Penassay Br.	10.0
Salmonella	Penassay Br.	5.0–10.0
M. tuberculosis	7H10	0.1–0.5
M. kansasii	7H10	0.2–1.0
M. intracellulare[1]	7H10	.04–2.5
M. intracellulare[2]	7H10	$\geq$10.0

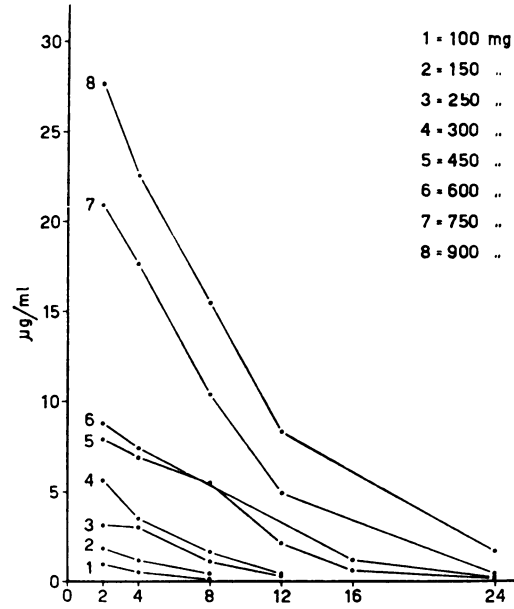

FIG. 2. Mean Serum Concentrations after Oral Dose of Rifampin.

reflects a 2-3 hour peak concentration 20–25 per cent higher and equivalent to 10–50 time the *in vitro* M.I.C. for M. tuberculosis. The bacteriologic results are shown in the graph (Figure 4). Ninety per cent were negative from the 4th–6th month. It should be borne in mind that this was a 2-drug regimen used in some hard core treatment failures of conventional regimens. Side effects were minimal and consisted of occasional abnormalities of SGOT and alkaline phosphatase, and WBC below 4000/mm³ in 3 patients. In none of these patients was interruption of treatment or change of regimen necessary before completion of the 6-month observation period, and in each case the laboratory values returned to normal while the treatment regimen was continued.

In January 1969, we undertook a second pilot study in the same 6 VA

TABLE 2

Rifampin Susceptibility—Pretreatment

	MIC—Mcg/ml			
	0.1	0.2	0.5	1.0
#	14	16	6	4
%	35	40	15	10
Cumulative	35	75	90	100

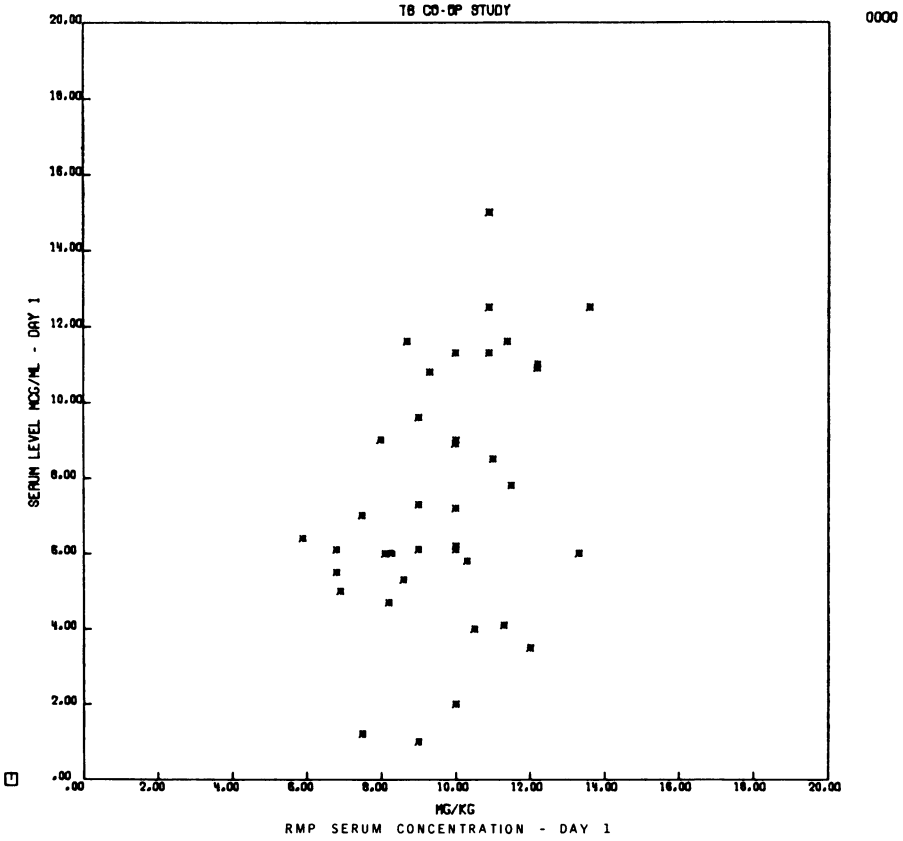

FIG. 3. Serum Concentrations of Rifampin on Day 1–4 Hours after Single 600 mg. Dose.

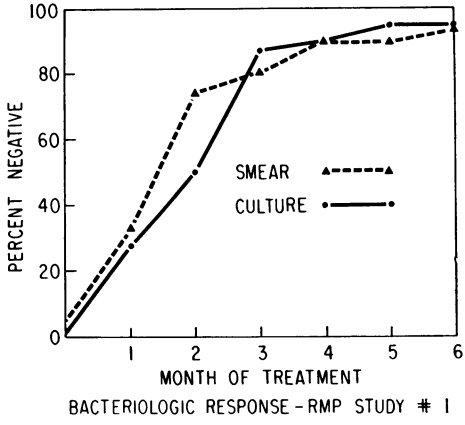

FIG. 4. Bacteriologic Response: Retreatment Study.

TABLE 3
Study Population

A. Eligible
   1. Advanced Pulmonary Tuberculosis
      a. Multiple cavities or
      b. Single cavity > 4.0 cm in diameter
      c. Sputum positive—smear and culture
   2. No prior antimicrobial therapy for tuberculosis
B. Exclusions
   1. Major renal, hepatic or 8th nerve dysfunction
   2. M. tuberculosis resistant to SM, INH or RMP before treatment
   3. Mycobacteria other than TB in sputum
   4. Females of childbearing age

Hospitals involving previously untreated patients with advanced tuberculosis. Table 3 shows the criteria for admission to the study. Patients were allocated at random to 1 of 3 treatment regimens:

1. Streptomycin 0.5 gm./d plus INH 300 mg./d
2. Rifampin 600 mg./d plus INH 300 mg./d
3. Streptomycin 0.5 gm./d plus Rifampin 600 mg./d.

Of 137 eligible patients admitted to the study, 22 failed to complete the 6-month treatment period on the assigned regimen. Eight left the hospital prematurely against advice, 4 died of non-tuberculous causes during the 1st month of treatment, 4 had regimen changes because of failure to improve on the assigned regimen, and 4 had their regimen changed because of drug side effects. Two of the latter had abnormal liver function tests which on subsequent challenge were clearly shown to be due to isoniazid. One developed hypersensitivity to streptomycin with fever and rash, and the 4th developed severe vertigo with loss of response to caloric stimulation which was attributed to streptomycin. Table 4 shows the rifampin susceptibility of pre-treatment cultures. All were completely inhibited by 1.0 mcg./ml., and 90 per cent by 0.5 mcg./ml. on 7H10 medium. Serum concentrations of rifampin were not determined for the patients in this study. The bacteriologic response to treatment in 115 patients who completed 6 months is shown in Figure 5. Ninety-two per cent of patients receiving the control regimen, SM-INH, 98 per cent of patients receiving Regimen 2, INH-RMP, and 88 per cent of patients receiving Regimen 3, SM-RMP, had negative cultures reported for the 6th month. The only point at which these differences are statistically significant is at the 3rd month point, when 86 per cent of those on Regimen 2 were negative compared with 52 per cent on the control regimen. On Regimen 1, 4 patients yielded isoniazid-resistant cultures during treatment and 1 of them was also resistant to streptomycin. On Regimen 3, 3 patients yielded cultures resistant to streptomycin during

TABLE 4

Pretreatment Susceptibilities—RMP

Hospital	MIC—Mcg/ml				
	0.1	0.2	0.5	1.0	5.0
1 (36)	4	27	36	36	36
2 (23)	7	12	20	23	23
3 (18)	14	11	17	18	18
4 (06)	1	6	6	6	6
5 (32)	14	22	32	32	32
6 (16)	0	0	8	16	16
Total 131	40	78	119	131	131
% 100	30	60	90	100	100

treatment and 1 to rifampin. On Regimen 2, 1 patient, the only failure, yielded isoniazid resistant cultures from the 12th week onwards but his cultures remained susceptible to rifampin.

The patients were screened pre-treatment and during treatment for drug side effects. White blood cell and differential counts were done weekly, and Table 5 shows that 13–15 per cent of patients had 1 or more WBC count below 4000/mm^3 reported during treatment. In none was a WBC count below 3000/mm^3 reported. Most of these were occasional or isolated findings, and in every instance the WBC count returned to normal while the treatment regimen was continued. There was no inter-regimen difference in the

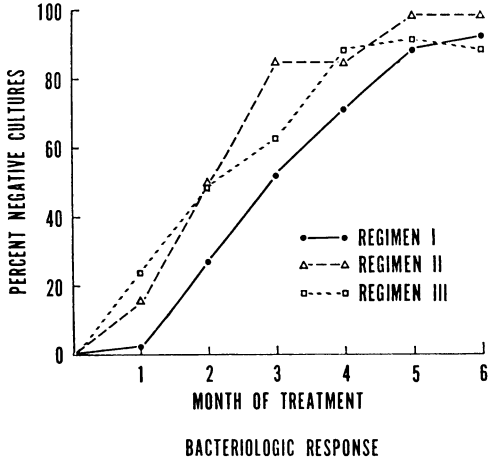

FIG. 5. Bacteriologic Response in Previously Untreated Patients.

TABLE 5

	WBC < 4000/mm³—Patients		
	Reg. I SM-INH	Reg. II INH-RMP	Reg. III SM-RMP
Initial	0	0	0
During Treatment	7 (15%)	6 (13%)	6 (13%)
Total	46	46	45

TABLE 6

	WBC < 4000/mm³—Patients							
	Reg. I SM-INH		Reg. II INH-RMP		Reg. III SM-RMP		Total	
	#	%	#	%	#	%	#	%
Caucasian	1/24	4.0	3/30	10	1/29	3.5	5/83	6
Negro	6/20	30	3/15	20	5/15	33	14/50	28

frequency of this finding. When the study population was broken down into Negro and Caucasian, leukopenia, usually granulocytopenia, was observed 5-6 times more frequently in black patients than in white but again no significant inter-regimen differences for either ethnic group (Table 6). Determinations for SGOT, alkaline phosphatase, serum bilirubin, uric acid were also carried out at monthly intervals. In 15–30 per cent of patients sporadic elevations of laboratory values above normal were noted but in no instance was a significant inter-regimen difference observed. The explanation for these observations in laboratory findings is not entirely clear, but our impression is that they have more to do with the population in our study than with any specific chemotherapy regimen.

Discussion and Conclusion

Our impression thus far is that rifampin is an antimicrobial agent of the first order in the treatment of tuberculosis and is very well tolerated by most patients. Hepato-toxic side effects have unquestionably been demonstrated by others, but such side effects clearly attributable to the drug were not observed in our studies. More recently attempts to use rifampin in high dose, intermittent treatment regimens have been associated with some rather disturbing side effects, which seem pretty clearly attributable to rifampin. These have consisted principally of hypersensitivity reactions, sometimes associated with the development of complement fixing antibodies in the serum and in a few cases thrombocytopenia and purpura. Whether the high individual doses with high peak serum and tissue levels or whether

the intermittent schedule of administration is responsible for these occurrences is still not clear. Until these points are clarified, its use should probably be confined to a daily regimen using a conventional 600 mg. daily dose. In our hands such a regimen has proven thus far to be both effective and safe in the treatment of tuberculosis.

DISCUSSION

DR. THOMAS C. CHALMERS (Bethesda): I should like to compliment Dr. Raleigh and the Veterans Administration for this beautifully controlled study and point out that it must be about 20 years now since the VA first started to investigate the chemotherapy of tuberculosis in well controlled studies and that in these twenty years they have demonstrated so beautifully that long term, well controlled therapeutic trials can be done. New drugs can be introduced with scientifically precise controlled methods, and extremely useful results obtained as we have seen from this study.

DR. THEODORE E. WOODWARD (Baltimore): It might be interesting to point out that rifampin has provided the first new enthusiasm for treatment of patients with leprosy and it is amazingly effective. The organisms are fragmented soon after the drug is given. The problem of resistance to the sulfones, after five years or more of treatment, has plagued leprologists. Hence, rifampin has an important role in this related mycobacterial infection.

Dr. Raleigh, your paper was very instructive. Could you tell us if rifampin is to remain so expensive, or is there a chance of reduction in price?

DR. RALEIGH: I'm afraid I'm not privy to the inner councils of the Dow Chemical Company or Ciba so I don't know how long it's going to remain expensive. I can only say that as long as it does remain expensive, its use is going to be limited. I think the manufacturers will soon recognize this and make the necessary adjustments. I'd like to thank Dr. Chalmers for his comments and say that it is just 25 years this year since the first controlled study on chemotherapy was undertaken by the VA in 1946.

DR. JOHN P. UTZ (Richmond): The results you are getting in tuberculosis are very encouraging, Dr. Raleigh. It's nice to hear about these. For some reason that I'm not aware of, we have recently had in our hospital four cases of tuberculosis meningitis, one of which ended disastrously just last week. We can give the INH and streptomycin intramuscularly, but we are wondering if we are achieving anything at all by emptying out the capsules of rifampin and putting the drug down by stomach tube. I wonder if you or your group have any knowledge of the use of rifampin parenterally in such sick patients.

DR. RALEIGH: I don't know about parenteral rifampin itself, but the parent rifamycin drugs have the same general antimicrobial spectrum as rifampin itself and are given parenterally. If parenteral therapy is needed, I think, the rifamycins would be the drug to use rather than rifampin itself. After oral administration rifampin does appear in the cerebrospinal fluid particularly in patients with meningitis. It peaks in C.S.F. at about six hours instead of at 2–3 hours when it peaks in the serum. If one were to take simultaneous three-hour serum and cerebrospinal fluid levels one might find the cerebrospinal fluid level considerably lower than it will eventually become.

DR. ROBERT AUSTRIAN (Philadelphia): It might be worth pointing out that this drug is also licensed now for the treatment of the meningococcal carrier state as the only drug that has shown comparable efficacy to sulfonamides. The chief difficulty lies in the fact that rifampin-resistant meningococci emerge with considerable fre-

quency. If this drug is used promiscuously for this purpose, we will soon be confronted with the same problem that exists now with meningococci and sulfonamides.

DR. THOMAS F. FRAWLEY (St. Louis): In describing the drug's toxicity you remarked on the occurence of leukopenia. I was struck by what appeared to be a difference between the frequency of leukopenia in the negro patients as compared to the white patients. I noted after moving to St. Louis that we were encountering what appeared to be more leukopenia from propylthiouracil than I had been accustomed to seeing while located in the eastern part of the United States. A review of the hospital records indicate that this apparent increase in frequency was limited to negroes. Dr. G. O. Broun, Jr., of our Section of Hematology, has made a study of the white cell counts in healthy negroes in the St. Louis area. He reported (*N.E.J.M.* **275:** 1410, 1966) that approximately 25 percent of them have a significant leukopenia due to granulocytopenia and concludes that this is normal for such individuals. This finding has been confirmed in studies of other populations of negroes in the United States and in foreign countries. Therefore, the point I wish to make is that it is important to keep in mind that leukopenia is a normal occurrence in some negroes and that one must know the base level of the white-cell count in any patient before concluding too hastily that a particular drug induces significant leukopenia. Otherwise, approval may not be granted on this basis for a potentially valuable therapeutic agent.